## REMARKS

A check for the fee for a three month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A supplemental Information Disclosure Statement has been filed under separate cover.

Claims 45, 46, 62, 70, 78, 94, and 96-104 are pending in this application. Claims 101-104 are added, and find basis throughout the specification, for example, at Table beginning at page 46 to page 49, and at page 72, lines 1-16. No new matter is added.

Claims 45, 46, 62, 78, 96 and 97 are amended for clarity, for example, to provide antecedent basis. Claims 62, 96 and 97 also are amended to correct reference to nucleic acid position and SEQ ID NOs. Basis for these amendments can be found throughout the specification, for example, at page 31, lines 18-19; at Table beginning at page 46 to page 49; at Table beginning at page 53 to page 63; and in the Sequence Listing. In addition, claim 45 is amended by addition of the term "standard conditions," to render it clear that the mutation is one that increases expression under the conditions in which AAV is normally expressed. Basis for such is found throughout the application, which describes preparation of AAV under such conditions. There is no discussion in the application of temperature sensitive mutations that produce AAV under non-standard conditions nor growing AAV under non-standard conditions. The application, insofar as it is directed to AAV, is directed to identifying Rep mutants that result in increased titer compared to wild-type under standard conditions. Hence, such is implicit in the application (see e.g., *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973); also see e.g., *In re Saunders*, 444 F.2d 599, 607. 170 USPQ 213, 220 (CCPA 1971); *In re Johnson,* 558 F.2d 1008, 194 USPQ 187 (CCPA 1977).

Applicant respectfully submits that the instant specification is directed to nucleic acid molecules encoding mutant Rep proteins that result in high-titer rAAV stocks for use in, for example, gene therapy. A reading of the specification as a whole renders it clear that the mutant molecules result in a higher titer of rAAV compared to wild type encoded Rep proteins under conditions where the wild-type Rep proteins are tested, *i.e.* standard conditions. All tests were performed at 37 ° C, and comparisons between and among the mutant Rep proteins all were preformed under such conditions.

For example, the specification describes that a problem solved by the instant application "is a solution to the need in the gene therapy industry to increase the production of therapeutic vectors without up-scaling manufacturing," (see page 4 , lines 22-25) and that methods provided in the specification to identify mutant molecules "permit optimization of its activities as assessed by increases in viral production" (see page 28, lines 9-11). Clearly , this does not include production at 32° C, which is a temperature that one of skill in the art would not normally transfect mammalian cells and/or produce virus, and therefore is a condition which one of skill in the art would recognize to be improper for providing rAAV stocks with higher titers. Further, as discussed throughout the application, all 566 mutants that were prepared were tested and compared to wild-type AAV at standard temperature for the wildtype, not at reduced temperature. Accordingly, amended claim 45 reflects that the comparison is effected at standard conditions for expression of the wildtype virus. Furthermore

> By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Thus, no new matter is added.

**Restriction Requirement and Election of Species**

Applicant acknowledges that claims 45, 46, 62, 70, 78, 94 and 96-100 are pending and under examination. The Examiner, however, urges that the instant claims are under examination only with respect to the mutation identified in claim 62 as "T to N at position 350" represented by SEQ ID NO:113, since no generic or linking claim is found allowable. As described herein below, Applicant respectfully submits that claim 45 as amended, and claims dependent thereon, are not anticipated by the cited reference. Accordingly, the Examiner is required to continue searching the species or additional species until art is found or until a reasonable number of species is searched.

**I. THE REJECTION OF CLAIMS 45, 46 AND 62 UNDER 35 U.S.C. §101**

Claims 45, 46 and 62 are rejected under 35 U.S.C. §101 for allegedly being directed to non-statutory subject matter. The Examiner alleges that the claims do not sufficiently distinguish over mutant AAV encoding a mutant Rep protein or cells that exist naturally within an animal body and that are infected with the mutant AAV encoding a mutant Rep

protein. In particular, the Examiner urges that the claims do not point out any non-naturally occurring differences between the claimed products and the naturally occurring products, and thus encompass a naturally occurring virus and a naturally occurring cell infected by the virus within an animal body. This rejection is respectfully traversed with respect to claims 45 and 62. The rejection is moot with respect to amended claim 46 (and claim 78).

It respectfully is submitted that the claims are directed to nucleic acid molecules encoding **mutant** adeno-associated virus (AAV) Rep protein that have increased activity compared to a wild-type Rep, and hence do not read on nucleic acid molecules that exist in nature. Claim 45 recites:

> A nucleic acid molecule that encodes a **mutant** adeno-associated virus (AAV) Rep protein that has increased activity, wherein:
>
> increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication of virus under standard conditions for wild type virus production in a host cell, that contains in its genome the nucleic acid molecule encoding the mutant Rep protein, compared to the titer of virus upon introduction and replication of a virus in a host cell containing a wild type Rep gene;
>
> the AAV serotype is an AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4 or AAV6 serotype; and
>
> the mutation is in the corresponding position in each serotype.

Dependent claim 62 recites specific mutations.

Hence, contrary to the statement by the Examiner, the claims do point out a non-naturally occurring difference between the claimed products and the naturally occurring products, *i.e.* a mutation in the nucleic acid molecule encoding a mutant Rep protein such that a host cell containing the nucleic acid molecule has an increased viral titer compared to a host cell containing a wild type Rep gene. The Examiner has provided no evidence that such mutations exist in nature. Thus this rejection is not apt.

As noted in the response mailed December 29, 2006, a rejection under 35 U.S.C. §101 is generally only made where the claims do in fact read on molecules as they exist in nature. For example, "a nucleic acid molecule encoding erythropoietin" reads on a nucleic acid molecule as it exists. Since the molecule was originally isolated from a natural source, it is unequivocal that it exists. This is different from the instant claims, which are directed to mutant molecules created *in vitro* and selected by particular assays.

## II. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 45, 46, 62, 70, 78, 94 and 96-100 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for various reasons as set forth below. Based on the remarks set forth below, Applicant respectfully requests reconsideration of these rejections.

**Relevant law**

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

**Analysis**

**A. Claims 45, 46, 62, 70, 78, 94, and 96-100**

Claims 45, 46, 62, 70, 78, 94 and 96-100 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for the recitation in claim 45 of "replication in a host cell of virus, in its genome" because it is not clear if reference is to the cell genome or the viral genome. It is respectfully submitted that claim 45 as amended renders it more clear that the **host cell** contains in its genome the nucleic acid molecule. Accordingly, Applicant respectfully requests reconsideration of this rejection.

In addition, claims 45, 46, 62, 70, 78, 94 and 96-100 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for the recitation in claim 45 of "equivalent position" because it is not clear whether the equivalent positions are structural equivalents or functional equivalents. This rejection is moot by the amendment of claim 45 herein to recite "corresponding position." Applicant respectfully submits that the term "corresponding position" is clear. For example, the specification defines "corresponding position" on page 18, line 3 as follows:

> As used herein, a "corresponding" position on a protein, such as the AAV rep protein, refers to an amino acid position based upon alignment to maximize sequence identify.

Hence, a corresponding position is with reference to the sequence alignment of the Rep protein in AAV serotypes. Corresponding positions in AAV serotypes are shown in

Figures 3A and 3B, which show alignment of AAV serotypes AAV-1, AAV-6, AAV-3, AAV-3B, AAV-4, AAV-2 and AAV-5 with reference to amino acid positions in the Rep78 protein. The corresponding positions in each of the AAV serotypes are further set forth in the Table beginning at page 49 of the specification. Thus, Applicant respectfully submits that the term is clear.

**B. Claims 62, 70, 78, 94, 96, 99 and 100**

Claims 62, 70, 78, 94, 96, 99 and 100 are rejected under 35 U.S.C. §112, second paragraph as being indefinite because it is allegedly unclear what "the corresponding residues" or "corresponding codon" in the other serotypes. The Examiner urges that a corresponding residue/codon can mean a residue codon at the same position within the protein or a residue/codon in a corresponding functional domain that is not necessarily in the same position. It is respectfully submitted that this rejection is moot by the amendment of the claims herein to recite the term "corresponding position." As described above, the Applicant clearly and in great detail describes corresponding positions of AAV serotypes based on sequence alignment.

**C. Claims 96, 99 and 100**

Claims 96, 99 and 100 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for the recitation in claim 96 of "AAV-7" or "corresponding codon replacements" because there is insufficient antecedent basis for these limitations in the claims. Applicant respectfully submits that this rejection is inapt with respect to claim 100, which does not recite, nor is dependent on a claim that recites, the term "AAV-7." Notwithstanding this, the rejection is moot by amendment of the claims herein.

Claims 96, 99 and 100 are also rejected under U.S.C. §112, second paragraph as being indefinite because it is not clear from the language of the claim whether Applicant recites the claimed nucleic acids in alternative, combination, or all together. Applicant respectfully submits that this rejection is inapt with respect to claim 100, which is dependent on non-rejected claim 97. With respect to claims 96 and 99, claim 96 is amended herein to render it clear that the nucleic acid molecules are claimed in the alternative.

**III. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH – WRITTEN DESCRIPTION NEW MATTER**

Claims 96, 99 and 100 are rejected under 35 U.S.C. §112, first paragraph for lack of written description because it is alleged that there is no disclosure for a nucleic acid molecule encoding Rep protein from AAV-7. Applicant respectfully submits that this rejection is inapt

with respect to claim 100, which does not recite, nor is dependent on a claim that recites, AAV-7. Notwithstanding this, Applicant respectfully submits that this rejection is moot by deletion of the term AAV-7 from claim 96.

**IV. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, FIRST PARAGRAPH – WRITTEN DESCRIPTION- POSSESSION**

Claims 45, 46, 62, 70, 78, 94 and 96-100 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that Applicant was not in possession of the full genus because the claims encompass a wide and variable genus of nucleic acid molecules, the structure of which is not sufficiently disclosed in the specification and the claims.

This rejection is respectfully traversed. As discussed below, the application identifies and provides examples of at least 12 species of nucleic acid molecules encoding mutant REP proteins that when expressed result in AAV with higher titer. The specification provides detailed description how to isolate and prepare additional species that have the requisite property. The application is directed to methods for preparing proteins with predetermined properties. Hence, applicant had possession of the genus of molecules as required by 35 U.S.C. §112, first paragraph. The remarks of the Examiner are rebutted in turn below.

**Relevant Law**

Relevant law and a discussion of the Patent Office Guidelines are set forth in previous responses of record. Briefly, the purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.,* whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir. 1989).

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem*, 323 F.3d at 963, 63 USPQ2d at 1613. MPEP §2163. Further, as noted above, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012. Thus, the

knowledge and level of skill in the particular art is a factor to be considered in determining the standard.

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a parent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443, F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).

**The claims**

Claim 45 is directed to a nucleic acid molecule that encodes a mutant AAV Rep protein, in any AAV serotype of AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4 and AAV-6, that has *increased* activity as manifested as an increased titer of virus upon introduction and replication of virus in a host cell containing in its genome nucleic acid encoding the mutant Rep protein, compared to the titer of virus upon introduction and replication of virus containing a wild type Rep gene. The claim specifies that the mutation is in the corresponding position in each serotype. All other claims are dependent, directly or indirectly, on claim 45. For example, claim 62 is directed to a nucleic acid molecule of claim 45 and specifies specific amino acid replacement in an encoded Rep protein.

**Analysis**

The Office Action alleges that there is a lack of written description of the claimed genus of nucleic acid molecules encoding mutant Rep proteins having increased activity. It is alleged that insofar as the genus of nucleic acids encoding for mutant Rep proteins is very large and a great deal of variability is encompassed by the instant claims, the claims encompass within their breadth any nucleic acid encoding for a mutant Rep protein that has increased activity. In particular, the Examiner urges that the genus is described by its function to affect viral replication, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Accordingly, it is alleged that Applicant is not in possession of the claimed subject matter at the time the application was filed because the specification fails to provide the

relationship between structure and function for the nucleic acids encoding the mutant proteins. Applicant respectfully disagrees.

As discussed in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (hereinafter the Guidelines), the written description requirement for a claimed genus may be satisfied through 1) sufficient description of a representative number of species by actual reduction to practice, 2) reduction to drawings, or 3) by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

It respectfully is submitted that the specification satisfies the written description guidelines through each of 1-3 above by (1) describing a representative number of species by actual reduction to practice and by providing data that demonstrates increased viral titer; (2) providing the sequences of such molecules and corresponding positions in other AAV serotypes; and (3) providing the relevant identifying characteristics of the claimed nucleic acid molecules, i.e. modified nucleic acid molecules that encode Rep proteins that result in increased titer of AAV. As discussed below, the application tested **every amino acid locus** to identify **all** whose change results in a change in titer. Every replacing amino acid was tested. Hence the application provides a detailed description of the relationship between the structure and functioning of Rep proteins as assessed by assessing viral titer. Based on this property and using the methods as described, the application teaches how to identify any additional species within the scope of the claim and how to assay or test combinations of mutations. The application describes a method for preparing proteins that have predetermined properties and exemplifies it using the AAV Rep proteins. In fact, the application exemplifies an **entire genus** with respect to one serotype and identifies the corresponding mutations in all other AAV serotypes. Thus, Applicant possessed the claimed subject matter at least as of the filing date of the instant application.

As discussed below, the application provides a detailed description of identification and preparation of a representative number of such nucleic acid molecules encoding mutant Rep proteins, including detailed description and working examples and of the method for generating such molecules and testing such molecules. Furthermore, the specification provides methods for producing and testing additional modified Rep proteins and nucleic acid

molecules encoding the same for increased viral titer. Hence, Applicant possessed the genus as claimed.

**A. The specification provides sufficient identifying characteristics of nucleic acid molecules encoding mutant Rep proteins to evidence Applicant's possession of the claimed subject matter as of the filing date.**

An adequate written description of a claimed genus need provide "relevant, identifying characteristics" sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention (MPEP §2163). The Enzo court stated that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" Further, the Guidelines set forth that a relevant identifying characteristic can be stated in terms of a function. For example, the Guidelines state as follows:

> For example, if the art has established a strong correlation between structure and function, one skilled in the act would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of a function and minimal structure when there is a well-established correlation between structure and function. MPEP §2163.

In this instance, Applicant respectfully submits that the claimed nucleic acid molecules sufficiently are described based on an identifying characteristic shared amongst the genus of claimed molecules, i.e. the feature of increased viral replication. The specification describes in great detail how to identify such molecules, and exemplifies representative species, including their sequence, that exhibit this identifying feature. Applicant is providing mutants that have *increased* activity as manifested by increased viral titer. The application tested every single position, using every amino acid replacement at each locus, in one serotype and tested the effect on the resulting AAV viruses. Hence for AAV-2, every member of the genus is identified and tested. The application prepared and tested every combination of modified amino acid (see, *e.g.*, the Example and Figures) for each of the Rep proteins and identifies the loci that contribute to changes in viral titer. The application further identifies those loci and amino acid changes that result in increased titer. Further, the application identifies the corresponding loci in all AAV serotypes. In addition, the

application teaches how to prepare additional mutants and test them. The application provides the structure/function relationships.

The application provides a very detailed description of how to modify Rep encoding nucleic acids, and, in fact modifies every single amino acid in the proteins one-by-one and tests the effects. The application teaches (see, *e.g.*, page 28) that the Rep protein(s) are involved in replication and are the target for the methods in the application for increasing viral production. As stated in the application (page 28), the methods in the application permit optimization of the activities of Rep as assessed by viral production. The methods tested every amino acid locus on the Rep protein and identified those that lead to a change in activity (i.e. those relevant for viral replication). The alanine scan across the full length of the Rep-encoding nucleic acid molecule identified hit loci. Each hit locus was replaced with the 18 remaining amino acids one-by-one; each molecule was tested one-by-one, so that each locus and amino acid change leading to increased titer was identified (see *e.g.*, page 29 *et seq,* the Example, and Figures 2 and 3; amino acid sequences of all Rep proteins are set forth in SEQ ID Nos. 1-562 and 726-728 and of the nucleic acid molecules SEQ ID Nos. 563-725) The application describes assays for assessing titer. In both rounds of testing, each mutant was individually designed, generated, processed and tested. Page 31, for example, summarizes the results, identifying all hit positions for reach of the Rep proteins. The application identifies, for the first time, mutations, including replacing amino acids, that increase viral titer (under standard conditions).

The specification describes in great detail the generation of and testing of nucleic acid molecules encoding mutant Rep proteins for viral replication to identify those that encoded proteins that resulted in an increased viral titer. For example, the specification describes a mammalian cell-based expression based assay to phenotypically characterize the mutants for effects on viral titer. The specification describes all the necessary components of the assay used to generate recombinant (rAAV) viruses containing nucleic acid molecules encoding the mutant Rep proteins, and the assessment of the viral titer of the produced rAAVs. For example, the specification describes the generation of rAAV viruses by the co-transfection of mammalian cells with three plasmids: a plasmid encoding the mutant Rep proteins, a plasmid encoding AAV necessary proteins and DNA and an rAAV plasmid vector that provided the necessary signaling and substrate ITR sequences.(at page 30, line 1-14). The specification further describes the assessment of viral titer of each rAAV generated by determination of the number of infection particles (ip) produced by each rAAV upon introduction of the virus into

a mammalian cell using either a reporter gene (i.e. bacterial lacZ) or real time (RT)- PCR readout (see e.g., at page 30, lines 21-24). This is exemplified in the Example. Other assays for the determination for viral titer are known to one of skill in the art. The specification, including the Example, describe the testing of a variety of nucleic acid molecules encoding mutant Rep proteins and exemplify 12 clones having increased activity as manifested by increased viral replication (see e.g. Figure 2B).. The specification describes the corresponding position of the encoded mutations in each of the seven AAV serotypes.

The specification clearly describes that other mutants and other combinations of mutants can be generated and identified. For example, the specification at page 33, lines 3-8 states:

> Other combinations of mutations can be prepared and tested as described herein to identify other leads of interest, particularly those that have increased rep protein activity or that result in higher viral titers in cells containing such viruses that include appropriate cis acting elements for viral production.

Hence, the specification clearly set forth that Applicant had possession of a genus of nucleic acid molecules encoding mutant Rep proteins exhibiting effects on increased viral titer, and that such molecules could be identified by testing for viral activity.

Hence, the instant application clearly describes a genus of nucleic acid molecules encoding mutant Rep protein having a relevant identifying characteristic of increased activity as manifested by effects on increased viral titer. Because the specification adequately describes how one may (i) identify and select molecules that provide increased activity; (ii) generate the molecules; and (iii) measure a specific effect, namely effects on increased viral titer, Applicant had possession of the claimed subject matter at the time of filing the application.

**B. The specification exemplifies more than a reasonable number of species**

Applicant is not required to provide a representative of everything claimed but may show possession by providing identifying features common to all members. As described above, Applicant, by way of detailed descriptions of features, working example, and exemplary molecules, has done exactly that. Accordingly, Applicant respectfully submits that the specification sets forth a representative number of species of the claimed nucleic acid molecules, which species were actually reduced to practice, to evidence Applicant's possession of the claimed subject matter. According to the Guidelines, a ``representative number of species" means that the species which are adequately described are representative of the entire genus. As discussed, the application describes assessing the effect of changing

each and every amino acid position with every amino acid, and identifies those that result in increased titer and identified every position that contributed in increased titer and then identified the corresponding positions in all AAV serotypes. Applicant can do no more. The specification provides 12 loci in nucleic acids encoding mutant Rep proteins, that result in increased viral titer, Further, the specification sets forth corresponding mutations in each of the other AAV serotypes, thereby providing no less than 70 species of nucleic acid molecules encoding a mutant AAV Rep protein that have increased activity. This is based on testing and exemplifying 566 species.

Further, the Guidelines state the following:

> What constitutes a ``representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.

It respectfully is submitted that one of skill in the art would conclude that, having tested all combinations of mutations and providing the data for such tests the description in the specification constitutes a sufficiently detailed description to evidence that Applicant's possession of nucleic acid molecules that encode Rep proteins that result in increased titer compared to wild-type under standard conditions.

As discussed in each of the previous two responses, the Examiner has failed to indicate why one of skill in the art, who is in possession of the nucleic acid molecules encoding any one or more mutant Rep protein (via the overlapping nature of the reading frames), in view of the description in the specification of all of the tested species, including the Example, Figures 2 and Figures 3, which exemplify the sequence identity among AAV serotypes and corresponding positions, and of the methods for preparing and testing polypeptides for activity, in view of the extensive knowledge of those of skill in the art, would be unable to recognize, upon reading the disclosure, that Applicant has possession of the claimed subject matter at least on the day of filing of the priority application. The specification clearly exemplifies mutations in the AAV genome that result in increased viral titer, and teaches in great detail how to generate other such species.

**Rebuttal To Examiner's Remarks**

1) The genus (i.e. the nucleic acids encoding for mutant Rep proteins) is described by its function to affect viral replication, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally, the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different nucleic acids.

Applicant respectfully disagrees. First, as described in detail above, the specification clearly describes in great detail relevant identifying characteristic shared among all members of the genus of nucleic acid molecules, i.e. the feature of increased viral titer, to show that Applicant was in possession of the claimed genus of molecules. As discussed, the specification describes and provides the results of testing every locus in the Rep protein and the effect of changing each amino acid. The speciation identifies all loci that affect the resulting titer, including those changes that result increased titer. Thus, contrary to the Examiner's assertions, Applicant **has described** an identifying characteristic, such as specific attributes and functional attributes, of the different nucleic acid molecules. Not only has Applicant described the identifying characteristic, but Applicant also has exhaustively detailed how to test for the relevant identifying characteristic of increased viral titer to identify other molecules, and has tested 566 molecules. As discussed in detail above, and as set forth in the Guidelines, a description of a genus of molecules by disclosure of a relevant identifying characteristic is demonstrative of possession of a claimed genus.

Furthermore, there is no requirement that written description requires exemplification of structure per se, so long as there is an adequate correlation of structure-function. See also MPEP § 2163:

> ...there is no **per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.**" *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084 ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.).< For example, disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. *Noellle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004). Emphasis added.

The requirements of a structure-function relationship sufficient to establish written description of a claimed genus of **modified** molecules, where the molecules were described based by an identifying characteristic of functional activity, was addressed in *Invitrogen Corp. v. Clontech laboratories Inc.* (429 F.3d 1052, 77 USPQ2d 161 (Fed. Cir. 2005); hereinafter *Invitrogen*). Claim 1 of U.S. Patent No. 6,063,608 at issue in *Invitrogen* recites:

> An isolated polypeptide having DNA polymerase activity and substantially reduced RNAase H activity, wherein said polypeptide is encoded by a reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNaseH activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

The court in *Invitrogen* held that generically claimed reverse transcriptase produced by modifying known genes were adequately described in view of the disclosure of representative embodiments, disclosure of test data that the enzyme produced by the claimed sequence has the claimed feature of DNA polymerase activity without RNase H activity, and the fact that the starting genes were known in the art. Accordingly, the court in *Invitrogen* recognized that a specification need not disclose the structure of all claimed molecules so long as the biological materials claimed were obtained from material that were known and characterized prior to filing. Applicant respectfully submits that the instant specification, which identifies the loci that participate in the requisite activity, more than adequately meets the above standards.

2) Applicant is relying upon biological activity and the disclosure of eight mutants having increased activity to support an entire genus. It is well known that minor structural differences among even highly structurally related compounds can result in substantially different biology. The specification fails to disclose what requirements a nucleic acid must meet to encode mutant Rep protein with increased activity; i.e. the specification fails to provide the relationship between structure and function for the nucleic acids encoding the mutant proteins.

First, as discussed in detail above, the specification provides the results of testing modification of every locus in the Rep proteins and substitution of every amino acid at every locus. Applicant provides a detailed discussion of the hits and the effects of each amino acid change on activity. Hence, Applicant provides far more than eight mutants. Applicant for the first time identifies mutations that will contribute to increased titer, tests every locus, and provides methods and assays for testing any others and combinations thereof.

Second, it appears that the Examiner is urging that the written description is not satisfied because some embodiments might not be operative. It is respectfully submitted that this is not the correct standard for written description. The purpose of the written description requirement is to show that Applicant was in possession of the claimed subject matter. As described in detail above, written description can be satisfied by the disclosure of a relevant identifying characteristic, including a functional activity, that is representative of the genus of claimed molecules, and also by the presence of a representative number of species. Applicant is not required to provide all species encompassed within a species, or show that all function as claimed, in order to satisfy the written description requirement. In *Capon v. Eshar* (418 F.3d 1349, 76 USPQ2d, 1078 (Fed. Cir. 2005) the Federal Circuit addressed this in response to a decision by the United States Patent and Trademark Board of Appeals that it could not be known whether all the permutation and combinations covered by the claims would be effective for the intended purpose, and that the claims were too broad because they might include inoperative species. The Court held that "it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon*, 418 F.3d at 1349, 76 USPQ2d at 1085. In this instance, Applicant submits that exemplification of the effect of increased viral titer of 12 encoded mutant Rep proteins, and assays to demonstrate the effect in other molecules, satisfies this standard.

In this instance, all of the embodiments are operative. Claim 45 specifically requires that the modified Rep proteins result in increased titer. Hence there are no inoperative embodiments encompassed within the claim. As noted, the specification provides the results of testing every locus and identifies those whose modification alters titer.

3) While it is true that Applicant provides means for producing and testing additional mutant Rep proteins and nucleic acids and this can be accomplished by routine experimentation, the fact that one of skill in the art would require additional experimentation is proof that applicant was not in possession of the claimed genus.

Applicant respectfully disagrees. As discussed above and in previous responses, the standard for written description is "whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." MPEP §2163. So long as one of skill in the art, by the disclosure of the specification, appreciates that

Applicant is in possession of the claimed genus, the written description requirement is met. Applicant is only required to provide a representative number of species, and not each and every species falling within a genus. In this instance, Applicant not only provided a representative number of species, but also provided description of a relevant identifying characteristic of the genus, and assays to test for other molecules based on the identifying characteristic. Hence, Applicant has more than satisfied the written description requirement.

**V. THE REJECTION OF CLAIMS 45, 46 and 94 UNDER 35 U.S.C. §102**

Claims 45, 46 and 94 are rejected under 35 U.S.C §102(b) as being anticipated by Gavin *et al.* (J. of Virol., 73: 9433-9445 (1999), which allegedly discloses a nucleic acid molecule encoding a mutant AAV-2 Rep78, wherein the mutant Rep protein has increased activity and wherein co-transfection of the nucleic acid encoding the mutant Rep and recombinant AAV plasmid into 293 cells mediates increased viral replication compared to the wild type. This rejection is respectfully traversed.

**Relevant law**

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

**The Rejected Claims:**

Independent claim 1 recites:

> A nucleic acid molecule that encodes a mutant adeno-associated virus (AAV) Rep protein that has increased activity, wherein:
>
> increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication of virus in a host cell under standard conditions for wild type virus production that contains in its genome the

nucleic acid molecule encoding the mutant Rep protein, compared to the titer of virus upon introduction and replication of a virus in a host cell containing a wild type Rep gene;

the AAV serotype is an AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4 or AAV6 serotype; and

the mutation is in the corresponding position in each serotype.

Dependent claim 46 recites:

An isolated cell, comprising the nucleic acid molecule of claim 45.

Dependent claim 94 recites:

The nucleic acid of claim 62, wherein the Rep protein is Rep 78, Rep 68, Rep 52 or Rep 40.

Hence, the claims are directed to a nucleic acid molecule that encodes a mutant Rep proteins that result in increased viral titer under standard conditions compared to a nucleic acid molecule encoding a wild type Rep gene, and isolated cells containing the nucleic acid molecule. It is unclear why claim 62 is rejected herein, since it is dependent on a non-rejected claim that recites specific mutations.

**Differences between the disclosure of U.S. Patent No. 5,785,970 and the rejected claims**

Gavin *et al.* discloses mutations in adeno-associated virus type 2 Rep78/68 by alanine substitution to target a number of the functional domains critical for Rep-mediated activities, and describe the effect of these mutations on Rep78-mediated replication of an ITR-containing vector in adenovirus-infected human cells. In particular, Gavin *et al.* discloses that a charge-to-alanine substitution strategy is particularly effective **to generate temperature sensitive (ts) mutants**. Gavin *et al.* discloses a temperature sensitive (ts) mutant, D40,42,44A-78, resulting in increased viral titer at 32° C. This mutant is defective for replication under physiological conditions. The mutant mediated replication 3-fold more efficiently at 32° C compared to at 37° C, and was essentially inactive at 39° C. At the permissive temperature of 32°C, the effect of the mutant on viral replication was delayed in adenovirus type 5-infected HEK 293 cells transfected with a plasmid expressing the mutant as assessed by Southern Blotting for Hirt DNA at various time points.

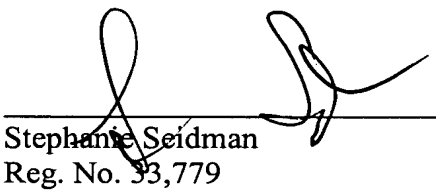
Gavin *et al.* discloses that, while virus was detected at normal levels in the presence of a wild-type Rep gene, there was *little to no detectable virus replication* observed at 37° C or 39°C in the presence of the encoded mutant Rep protein. Accordingly, the disclosure of Gavin et al. **does not** provide a nucleic acid molecule encoding a mutant Rep that has increased activity compared to a nucleic acid molecule encoding a wild type Rep protein

under standard conditions for expression of the wild type protein. Thus, Gavin *et al.*, does not anticipate claim 45, nor any claim dependent thereon.

* * *

In view of the, amendments and remarks herein, reexamination and allowance of the application are respectfully requested.

Respectfully submitted,



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